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Box-Behnken Statistical Approach For Development And Characterization Of Buoyant Oral Levofloxacin Tablets Using Natural And Synthetic Polymers

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ABSTRACT

Objective: The eradication of Helicobacter pylori infections is hampered by a number of factors, includingshort residence time antibiotics at the site of infection. This study developed a gastro-retentive buoyant tablets of levofloxacin by factorial experimental design approach with the ability to carry levofloxacin to increase its efficacy against H. pylori.

Materials and Methods: A three-level Box-Behnken statistical technique was used in this study to develop and evaluate buoyant oral Levofloxacin tablets using polymers such as guar gum and hydroxypropyl methylcellulose (HPMC) K100M and K4M. Several post-compression properties of the produced tablets were assessed, including hardness, friability, weight variation, floating lag time (FLT), swelling index (SI), and the time required to release 90% (T90%) of the medicine from the buoyant tablets.

Result: The following parameters were measured: thickness (3.18±0.10mm to 3.28±0.17mm), hardness (4.54±0.66kg/ cm2 to 4.85±0.20kg/cm2), friability (0.71±0.02g to 0.76±0.11g), weight variation (479±1.94mg to 518±0.72mg), swelling index (SI) (60.21±0.657% to 97.46±0.223%), floating lag time (FLT) (79.35±1.226 to 110.8±0.35s), and time required to release 90% of the drug from the tablet (T90%) (6.3±0.208h to 10.2±0.252h).Swelling was better with guar gum and HPMC K100M than with HPMC K4M.According to the study's findings, the HPMC K100M grade greatly impacted the drug release.

Conclusion: The designed gastro-retentive buoyant tablets were able to increase the amount of time that levofloxacin spends in the stomach and producing an effect of prolonged release. The oral drug delivery system consisting of levofloxacin buoyant tablets promise to be an effective approach for the complete eradication of H.pylori.

Keywords*: Three-level Box-Behnken statistical technique, buoyantlevofloxacin tablets, natural and synthetic polymers.*

INTRODUCTION

The helical, Gram-negative, flagellated bacterium known as Helicobacter pylori (H. pylori) affects over 4.4 billion individuals across the globe. The prevalence of H. pylori infection ranges from 85 to 95% in impoverished countries, while it ranges from 30 to 50% in industrialized ones. Initially, there were Helicobacter pylori is a recognized carcinogen, meaning it has been categorized as a "Class 1" infection by the International Agency for Research on Cancer (IARC) of the World Health Organization. Gastritis, gastric cancer, gastric ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue lymphoma are all possible outcomes of a Helicobacter pylori infection. Furthermore, H. pylori has been linked to non-gastrointestinal

diseases including diabetes, anemia, coronary artery disease, and coronary artery disease.[5-7] The specific way that Helicobacter pylori is transmitted remains a mystery, unfortunately. But it's been postulated that there are channels for transmission that involve the mouth and the face.[8-11]It is a known fact that approximately 95% of all gastric cancers are caused by *H. pylori*. Treatments for *H. pylori* eradication are widely used to minimise the risk of stomach cancer and related mortality, reduce the incidence of gastric cancer, and facilitate the healing of ulcers. Current guidelines state that patients with an active infection should get free of *H. pylori*. Unfortunately, many treatment regimens fail to eradicate *H. pylori* due to a lack of insufficient antibiotic concentration at the site of infection.[12] When *H. pylori* enter the stomach, bacteria use their urase activity to resist the unfavourable acidic environment. The bacteria use its flagella-mediated motility to travel in the direction of the stomach epithelium. Further interactions between *H. pylori* adhesins and the host cell receptors result in effective colonisation and infection. [13]Traditional drug delivery systems cannot provide sufficient concentrations of antibiotics to the infection site for a longer time because they do not remain in the stomach for long durations of time. For the reasons already stated, H. pylori cannot be fully eradicated by conventional therapy. Thus, novel drug delivery systems are necessary to remedy the drawbacks of conventional drug administration methods.[14-15]Floating drug delivery systems, or FDDSs, are also known as hydrodynamically balanced systems (HBS)(Tripathi, Thapa et al. 2019). To avoid the medications being emptied from the stomach too rapidly, FDDS uses drug carriers that float in the gastric fluid. The drug's availability in the stomach is increased for a longer length of time when its release is extended. Floating medication delivery devices are able to bypass the stomach's natural emptying pace for extended periods of time due to their reduced bulk density compared to gastric fluids (Erni and Held 1987). [16]The guidelinessuggest that levofloxacin-containing treatments are an effective first-line treatment. [17] Hence, gastro-retentive floating pills were created for the treatment of H. pylori to circumvent the shortcomings of the existing technique of levofloxacin administration. Guar gum, Hydroxypropyl methylcellulose (HPMC K100M), and Hydroxypropyl methylcellulose (HPMC K4M) were the ingredients used to make these tablets.

MATERIALS AND METHODS

Materials

The Mumbai-based company SD Fine Chem Limited supplied the guar gum. MICRO LABS LIMITED of Bengaluru provided the HPMC K100M and HPMC K4M, as well as the Levofloxacin hemihydrate. Additionally, only HPLC-grade solvents were utilized.

Experimental Design

A three-level Box-Behnken design with three variables and the Design-Expert® 13 application (Stat-Ease, Inc., USA) were utilized for optimization. Guar gum (C3), HPMC K4M (A1), and HPMC K100M (B2) were the three independent variables that were examined. The early trials sufficiently established the ranges for all three variables. The dependent variables that were chosen for this study are the following: Swelling Index (SI), floating lag time (FLT), and time necessary for 90% drug release from the tablet (T90%). These variables are listed in Table 1. Table 2 displays the experimental design and formulae.

The statistical model:

$$Y = b_0 + b_1A + b_2B + b_3C + b_{11}AA + b_{22}BB + b_{12}AB + b_{23}BC + b_{13}AC + E$$

Compatibility Studies

Using Fourier transform infrared spectroscopy and differential scanning calorimetry (DSC), we performed an examination of the excipient compatibility of levofloxacin.

Fourier transform infrared (FTIR) spectroscopy

Levofloxacin, excipients, and physical mixtures were measured in the 500-4,000 cm-1 range using a Fourier transform infrared spectrometer (FTIR 8400S; Shimadzu, Japan). The drug-to-excipient ratio was set at 1:1.

Differential scanning calorimetry (DSC)

The drug-to-excipient ratio was 1:1 when we examined Levofloxacin and its physical combinations with a DSC 204 F1 Phoenix® differential scanning calorimeter. Aluminum pans were used for the examination of 5 mg samples. The probes were subjected to a gradual heating process from room temperature to 400oC, with a nitrogen environment flowing at a rate of 50 ml/min.

Levofloxacin floating tablet formulation Levofloxacin, guar gum, sodium bicarbonate, citric acid, microcrystalline cellulose, magnesium stearate, and HPMC K4M and HPMC K100M were mixed in a mortar

with the following components in the amounts given; the mixture was then agitated for 5 minutes. The next step was to crush the mixture using a 9 mm standard flat-face punch in a proto press, which is a 10-station rotating tablet compression machine.

Characterization of floating Tablets

Test for Weight Variation

A digital scale (Mettler AE240 Erweka Tap) was used to measure twenty individual tablets in milligrams. Relative standard deviation, sample mean, and standard deviation were examined in relation to the weight data of the tablets.

Hardness

We measured the crushing strength of twenty different tablets using an Erweka hardness tester. It was determined the sample's mean, standard deviation, and C.V.

Thickness

Each of the twenty tablets had their thickness measured using a Digital Vernier calliper. The distances were measured. Coefficients of variation, standard deviation, and sample mean were computed.

Friability

The produced levofloxacin floating tablets were tested for friability using a Roche-type Friabilator. A hundred droplets were obtained by spinning a basket of fifteen dust-free tablets vertically in a Roche friabilator at 25 revolutions per minute for four minutes. This was done for the calculation. After dusting, we measured the tablets' total weight and used the following formula to calculate their percentage of friability:

$$\% \text{ Friability} = \frac{\text{Weight final} - \text{Weight initial}}{\text{Weight initial}} \times 100$$

Content uniformity

At random, ten pills were selected and their weights recorded. The 50 mL of 0.1 N HCl was used to dissolve each one after crushing it. The volume was increased to 50 ml using 0.1 N HCl prior to filtration. After proper dilution, the levofloxacin concentration in each tablet was measured by spectrophotometric testing at a preset wavelength of 294 nm. The label claim was compared to the content of each pill.

Floating Lag time measurement

We used the method developed by Rosa et al. to calculate the floating lag time. Three tablets were randomly selected from each batch and placed in a 500 mL beaker with 400 mL of 0.1N HCl. The floating lag time was determined by timing how long it took for the tablet to rise to the surface and float.

Total floating time measurement

We utilized the USP Dissolution equipment Type II (LAB INDIA) to determine the total floating time of the manufactured tablets. Hydrochloric acid at a concentration of 0.1N was added to 900 cc of pill containers. At a temperature of 37±0.2°C, the paddles were pulsated at 50 rpm. We visually documented how long the tablet stayed buoyant.

Swelling Index

The finished pills were placed in a beaker with 150 milliliters of 0.1N hydrochloric acid.The original weight of the pills was recorded before they were added to the beaker. We removed and weighed the bloated pills after 12 hours.Here is the formula that was used to get the swelling index:

$$\text{Swelling index } \% = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

***In vitro* dissolution studies**

A USP TYPE II paddle type apparatus from LAB INDIA was used to dissolve the produced floating tablets in 0.1N HCl. The samples were removed and replaced with new dissolving media at various intervals. All of the sample solutions were mixed with 10 milliliters of 0.1N hydrochloric acid before being subjected to spectrophotometric testing at 294 nanometers.[18-24]

Statistical analysis

Using Design Expert® 13 (Stat-Ease, Inc., USA) and a two-way analysis of variance (ANOVA), we determined the impact of each variable on the outcome. Response surface plots were generated to help see the impact of each variable on the response.

RESULTS AND DISCUSSION

Box-Behnken experimental design

A three-level Box-Behnken statistical design is comprised of fifteen trials in the RSM. Each of the fifteen experimental runs' independent variables and findings are listed in Table 2. The direct compression method was used to make the floating tablets of Levofloxacin. We measured and analyzed every single physical property for each formulation, including density, thickness, hardness, friability, and content consistency. For tablets with a weight more than 250 mg, the allowed fluctuation in weight is 5%, and the produced pills fell within this range. Furthermore, it was verified that all batches of tablets met the USP requirements for hardness and friability. Thickness was another determinant of tablet quality. All batches had thickness values between 3.18±0.10mm and 3.28±0.17mm, which was a permissible range. Table 3 provides the results. All formulations were Content Uniformity determined to have between 97.11% and 99.69% of Levofloxacin, which is under regulatory standards.The drug's compatibility with the excipients was investigated using instrumental methods including FTIR and DSC. In order to create FT IR spectra, levofloxacin, excipients, and physical mixes were used, with a drug:excipient ratio of 1:1. Pictured below are the outcomes (Figure 1). The following property was uncovered by the FT IR study of levofloxacin: highest points A range of 3255 cm-1 is associated with carboxylic group stretching, 2926 cm-1 with alkane group stretching, 1728 cm-1 with carbonyl group stretching, 1296 cm-1 with amine group stretching, and 1102-1398 cm-1 with halogen group presence. Image 1. The results show that levofloxacin is pure and identifiable, which is consistent with what Numan R. S. et al. found. The main peaks in the FTIR spectra of the pure medicine are preserved in the physical combination, with no noticeable peak shift. This rule out the possibility of process incompatibilities or drug-excipient interactions. [25]

Floating Lag Time

The flotation time of a tablet on a medium is known as FLT. The pill may be repositioned to the lower stomach region, where it may be gastric-emptied more quickly, as FLT increases. The duration of stomach transit for floating pills is influenced by FLT. This is why FLT should be avoided at all costs. All of the tablets used in the study were prepared using the effervescent technique. Gas was produced by reacting sodium bicarbonate with citric acid. Sodium bicarbonate and citric acid produce carbon dioxide when mixed with a dissolving agent (0.1 N hydrochloric acid). The carbon dioxide that is produced is contained within the tablet and is protected by the polymer gel that is formed when polymers are hydrated. This gel gives the tablets their buoyancy. [26] in The results of the FLT of Levofloxacin floating tablets are displayed in Table 4. The FLT (YFLT) fell within the range of 79.35±1.226 to 110.8±0.35s, according to the findings. Floating lag time is seen to grow with increasing polymer concentration, according to observations. Similarly, tablet floating lag durations are correlated with larger polymer concentrations. Just because it takes longer for polymers with larger concentrations to hydrate in the solution. The gas is therefore confined inside a gel barrier, which causes the floating tablet to travel upwards. When comparing tablets with different concentrations of HPMC K100M and guar gum, the floating lag time was shown to be smaller in the former. The results showed that HPMC K100M had the shortest floating lag time, followed by guar gum and HPMC K4M. The rate of hydration of this synthetic polymer is directly related to the percentage of hydroxypropyl substituents it contains. A extremely viscous gel is produced by HPMC K100M, which has the largest concentration of these groups compared to HPMC K4M. At the start of the release profile, this gel is very important for drug release. This may be because the polymers used in this study have a hydrophilic nature. Here is how the polymers' hydrophilicity was defined: There was HPMC K4M guar gum before there was HPMC K100M .[27]Due to a higher concentration of hydrophilic hydroxy propoxyl substitution rather than hydrophobic methoxyl substitution, HPMC K100M, the grade used in this investigation, hydrates at a faster pace than HPMC K4M. The pores may close too early, preventing the absorption of further fluids, since HPMC with a larger molecular weight expands more rapidly. Since it is more hydrophilic than HPMC K4M, HPMC K100M produces an instantaneous protective barrier when it hydrates. The formulation's high content of HPMC K100M causes it to float rapidly upon hydration. Solubility medium ingestion rate typically decreases with increasing HPMC molecular weight. Because of its higher hydrophilicity, guar gum hydrates faster and produces a protective barrier layer, shortening the floating lag time compared to HPMC K4M. Floating lag time differs between polymers due to differences in molecular weight and hydration state. [28]

Eliminating terms with a p-value greater than 0.05 from the model equations related FLT yields the following results:

$$FLT = 87.6933 + 6.17375*A + 8.06625*B + 7.0925*C - 2.5*AB - 1.7125*AC + 9.4025*BC + 6.01833*A^2 + 5.33833*B^2 + 1.97583*C^2$$

$$R^2 = 0.9705; \text{F value} = 18.30; P < 0.05$$

Swelling Index

The creation of novel materials for the improvement of drug delivery systems that offer prolonged drug release rates according to individual therapeutic requirements is a significant focus of research in the pharmaceutical sciences. An economical way to make new materials with interesting properties is to use mixes of existing polymers, as this cuts out a lot of the costs involved with making and studying entirely new materials. Another approach to creating polymeric materials with medicinal uses involves combining natural and manmade polymers. The need for innovative materials made of combinations of two or more polymers has skyrocketed throughout the past three decades. New biocompatible material classes with enhanced drug release control capabilities may be possible through the combination of synthetic and natural polymers. Synthetic polymers may include impurities, such as residual initiators, whereas natural polymers are often biocompatible. pp. [29–30] It is possible for both synthetic and naturally occurring polymers to possess useful properties. Biocompatible and biodegradable polymeric drug delivery systems with optimal drug release control capabilities may be synthesized by mixing or combining natural and synthetic polymers. The combination of natural polymer and HPMC has been detailed in several studies for its properties of sustained drug release. So, to maximize the swelling characteristic, this work used synthetic polymers. [31-32]The hydrophilic polymers known as hydrogels may soak up a lot of moisture. Their swelling creates a gel network that entraps and slows the release of the medicine, making them useful in drug delivery systems. One reason hydrogels are becoming more popular in drug delivery system formulations is that, when inflated, they may create a gel network that entraps the drug and prevents its release into the medium. Hydrogels are polymers with a high water-absorbing capacity. One essential attribute that affects the pace of drug release is the swelling ability of polymers. The swelling matrix's gel layer regulates the drug's dissolution and diffusion throughout the matrix, and it also controls the tablet's entrance of the dissolving media.sections [33–37]The research found that as compared to HPMC K4 M, guar gum and HPMC K100M shown better swelling. This could be because guar gum and HPMC K4M have different levels of hydrophilicity and hydration capabilities. The swelling rate of high-viscosity HPMC is higher than that of low-viscosity HPMC, as shown in investigations. Compared to HPMC of low viscosity grade, HPMC of high viscosity has a reduced ability to absorb water. [38] Swelling of polymers is greatly affected by the amount of water that enters the polymer matrix. When matrices absorb more water, the polymer matrix swells even more.One unit of HPMC is an ether-linked methoxyl and hydroxypropyl side group attached to a linear polysaccharide cellulose chain. There are several varieties of high-performance microcapsules (HPMC), each with its own unique chemical structure (substitution ratios and degrees), molecular weight, viscosity, and particle size. [39]

A range of 60.21±0.657% to 97.46±0.223% was noted for the swelling index. Triplicate runs of each experiment were carried out.

A range of 60.21±0.657% to 97.46±0.223% was noted for the swelling index. You may see the outcomes in Table 4.

This quadratic equation describes the impact of polymers on swelling index.

$$SI = 68.7833 + 5.18875*A + 7.815*B + 6.70125*C - 0.45*AB + 1.4675*AC + 7.695*BC + 12.9021*A^2 + 5.72958*B^2 - 2.44292*C^2$$

$$R^2 = 0.9631; \text{F value} = 14.49; P < 0.05$$

A significant model was developed (F value = 14.49: P value < 0.05). There is a reasonable match between the expected value of 0.4607 and the modified R2 value of 0.8966. The signal-to-noise ratio is what adequate precision is measured by. It is preferable to have a ratio higher than 4. There was a sufficient signal based on the calculated ratio of 11.312. The polynomial equation clearly shows that A, B, and C affect the swelling index. It was hypothesized that the swelling index would rise in tandem with the polymer concentration, given that all three independent variables (A, B, and C) had positive signs.

Drug Release

The dissolving investigation indicated that the amount of time required for the release of 90% of the medicine grew as the polymer concentration did as well. An increase in the quantity of swelling occurs as the final formulation contains more HPMC. Consequently, the drug's release is reduced since its diffusional path is lengthened. However, the gel layer thickness and swelling are both decreased when the HPMC level is reduced. Faster rates of drug release are made possible by this. The rate of drug release was observed to be much larger when comparing HPMC K4M to guar gum and HPMC K100M. The quick hydration of guar gum and HPMC K100M might be a contributing factor. The research indicates that there is an inverse relationship between HPMC concentration and gel formation. The drug's diffusion coefficient is affected by the polymer's viscosity as well. Quickly hydrating and rapidly forming a protective barrier, HPMC K100M has a higher hydrophilicity than HPMC K4M. By obstructing the dissolving medium from entering the tablet matrix, the medication release is diminished. As a result, the drug is released less slowly. Near zero-order release is usually not achieved with a single polymer alone, but rather with a combination of hydrophilic swellable polymers. This is because it is believed that these combinations are more likely to give the necessary release profile. [40] Therefore, guar gum was used for this work because, similar to HPMC, these natural polymers have demonstrated efficacy in maintaining drug release from a matrix system. [41-43]Similarly, our investigation found that medication release was impacted by HPMC grade. This occurs because matrices with greater viscosity grades swell more rapidly. Also, the amount of guar gum in the recipe affects T90%. Guar gum, when dissolved in water, may create hydrogen bonds due to its high concentration of hydroxyl groups. Guar gum's high viscosity, even at low concentrations, is caused by inter-molecular chain entanglement, which also gives it gelling and thickening capabilities in water. In addition to the mannose structure and galactose branches, there are even more exposed hydroxyl groups. When the mannose backbone is linked to the water molecules and galactose side chains in the surrounding area, intermolecular chain entanglement happens. [44-46]

The $T_{90\%}$ (time needed for 90% of the drug to be released) ranges was observed from 6.3±0.208 h to 10.2±0.252 h.

After removing insignificant components from the model equations connecting T90% as responses,

$$T_{90\%} = 7.13333 + 0.525{*}A + 1.1{*}B + 0.875{*}C - 0.025{*}AB - 0.025{*}AC + 0.675{*}BC + 0.895833{*}A^2 + 0.645833{*}B^2 - 0.154167{*}C^2$$

$$R^2 = 0.9669; \text{F value} = 16.23; P < 0.05$$

There is less than 0.2 between the adjusted R2 of 0.9073 and the projected R2 of 0.8024, indicating that the two are reasonably in agreement. A sufficient level of accuracy is defined as the signal-to-noise ratio. It is preferable to have a ratio higher than 4. With a ratio of 11.862, we have a sufficiently strong signal. The design space may be explored using this model.

Kinetic studies

The kinetics of drug release were determined by employing the Higuchi equation, the Korsmeyer-Peppas models, zero-order kinetics, and first-order kinetics. [47] In order to identify the type of release mechanism used, the data on medicine release were studied. The drug release mechanism is diffusion, as demonstrated by the fact that the zero-order, first-order, and Higuchi models all have the best agreement with the largest determination R2 coefficients. Diffusion, swelling, and erosion are the main mechanisms used to adjust the rate in controlled or prolonged release formulations. To prove that diffusion accounts for the vast majority of drug release from a polymeric system, Fickian diffusion is the gold standard. [48]

The usage of formulations containing swelling polymers, however, necessitates additional steps. Some of these processes include polymer chain relaxation, water-induced polymer elongation, and the glass-to-rubber phase transition. The diffusion limitations are changed when an object swells because its volume increases substantially. Korsmeyer and Peppas developed an equation to describe the transport process; they used this data, together with in vitro release data, to examine the release pattern. This formula elaborates on the finding that two seemingly independent drug transport channels can, in fact, be superimposed. The release of medicines from inflated polymers is described by both mechanisms—fickian diffusion and case II transport. The information about the release mechanism is provided by the value of n.[49-50]

Cylindrical tablets with N values less than 0.48 were thought to have a classic Fickian diffusion-controlled release mechanism, but those with n values more than 0.94 were thought to undergo swelling or erosion.

Non-Fickian transport including both processes was shown to happen for n values ranging from 0.48 to 0.94. The fact that our n values ranged from 0.48 to 0.94 suggests that the regulation of levofloxacin release was the result of many mechanisms. A link between swelling, erosion, and anomalous type diffusion—also known as non-Fickian diffusion—controlled it.

CONCLUSION

Floating tablets containing levofloxacin were effectively made utilizing HPMC K4M, HPMC K100M, and guar gum. The drug release profile, swelling ability, and floating lag time of the floating tablet were all improved using a Box-Behnken design. The gas-generating agent utilized in this investigation was a mixture of citric acid and sodium bicarbonate. Findings demonstrated that formulation variables, including HPMC K100M and K4M concentrations as well as guar gum, affected the floating characteristics and medication release of levofloxacin floating tablets. To better comprehend how both natural and synthetic gums impacted the medication release profile, response surface plots and polynomial equations were utilized. The drug release rate was affected by the polymers' viscosity and molecular weight. When comparing HPMC K100M to HPMC K4M and guar gum, the study found that HPMC K100M considerably helped regulate drug release. You may manage the release rate for up to 12 hours with HPMC K4M, HPMC K100M, and guar gum. This means that the right medication release profile may be achieved by combining natural gums with synthetic polymers, and then optimizing these polymers using the right procedures. Finally, the designed levofloxacin floating pills have the potential to extend the amount of time that levofloxacin stays in the stomach. The recently created levofloxacin floating medication delivery system has the potential to effectively eliminate H. pylori.

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